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Reply

We sincerely thank these correspondents for their keen interest in our work (1). Instantaneous wave-free ratio (iFR) would not have been possible without fractional flow reserve (FFR). The authors are strong supporters and regular users of pressure-derived indices of stenosis severity in their clinical practice, and they acknowledge the great impact that FFR has had on patient management. More than an independent index of stenosis severity, iFR constitutes a scientific attempt to get FFR-like measurements with further simplification of the technique, with the aim of facilitating adoption of physiology in the catheter laboratory and thus improving patient management. We are aware that FFR constitutes the current paradigm of invasive stenosis assessment, and therefore, we welcome the healthy criticisms and the hint of skepticism implicit in the 3 letters sent to the Editor, occasionally with some déjà vu of the initial reactions witnessed during the introduction of FFR.

Dr. Rudzinski and colleagues raise several excellent points. iFR and FFR do agree best at higher values. But where they disagree, historic teaching would be that FFR—in which resistance is aggressively minimized—should always have the lower pressure ratio. Actual observations are opposite to this. It is with relief that we find the mechanism for this has been extensively established in the physiology literature. Intense pharmacological vasodilator stimuli can disrupt natural regulatory mechanisms beyond their homeostatic range, and lead to a paradoxical increase in microcirculatory resistance by reducing coronary perfusion pressure (2). While previously obvious only in pressure flow studies, it can now be seen in the elevation of the Pd/Pa ratio by adenosine in FFR, because for the first time stable wave-free Pd/Pa can be measured (iFR) without pharmacological interference by adenosine. These paradoxical disturbances in resistance by adenosine are obvious in the severe range, but cannot be assumed to be absent in the rest of the wide spectrum. The Bland-Altman plot may have its upward tilt to the left explained by this.

The scatter of the Bland-Altman plot has little scope to be much narrower because, just as iFR comes with its intrinsic variability, FFR also has intrinsic variability, most elegantly described in the DEFER study, which showed that, within 10 min in the same patient in the same expert hands, an FFR of 0.86 initially could jump between 0.70 and 0.90 on repeated measure (3). For this reason, neither iFR, nor FFR, nor any other measure, could ever match FFR perfectly. Despite this, we are encouraged by the fact that the scatter of our plot was much narrower than that in the Bland-Altman plot, demonstrating the widely accepted excellent relationship between FFR to positron emission tomography (4).

Contrary to the opinion of Dr. Finet and colleagues, we found wave intensity analysis (WIA) a very useful tool to demonstrate in a scientific and objective way how to overcome the limitations imposed by using time-averaged pressures for FFR calculation. As a matter of fact, WIA revealed the limits of the nice metaphor used by Dr. Finet and colleagues depicting adenosine-FFR as a wind tunnel, showing that, contrary to the constant laminar flow used in a wind tunnel, constant variations ("bumps") occur in the coronary arteries as a result of waves generated from the aorta and the microcirculation over the cardiac cycle, with the exception of a short wave-free period within diastole that best fulfils the theoretical requirements of FFR. Once this wave-free period was identified, we compared the values of coronary resistance with those obtained with time-averaged pressures in FFR. The documented similarity of resistance values shown in Figure 5 of our paper (1), and not the absence of waves as such as suggested by Finet and coworkers, stands as the cornerstone of iFR. Although seldom found, FFR values around 0.2 can be found in clinical practice and in some of the foundational papers of FFR (3,5).

The statement by Dr. Pijls and colleagues that "the validity of iFR depends on the assumption that minimum resting myocardial resistance during diastole is equivalent to the mean resistance during maximum hyperemia" is incorrect. A more correct proposal would be that the validity of iFR depends on the demonstration that myocardial resistance during a specific part of diastole (iFR) is similar in stability and magnitude to that calculated from whole cycle averaged measurements during hyperemia (FFR). In our paper, we highlighted that the reduction in myocardial resistance in response to adenosine administration is largely due to a reduction in its systolic component, a key issue to understand why the resistances underlying FFR and iFR calculation are similar, but we did not propose that diastolic myocardial resistance remains completely unchanged during adenosine-induced hyperemia. However, if excessive resistance explained the difference between iFR and FFR, the numerical disagreement between them would be related to the difference in resistance between the 2 states. But it is not (Fig. 1).

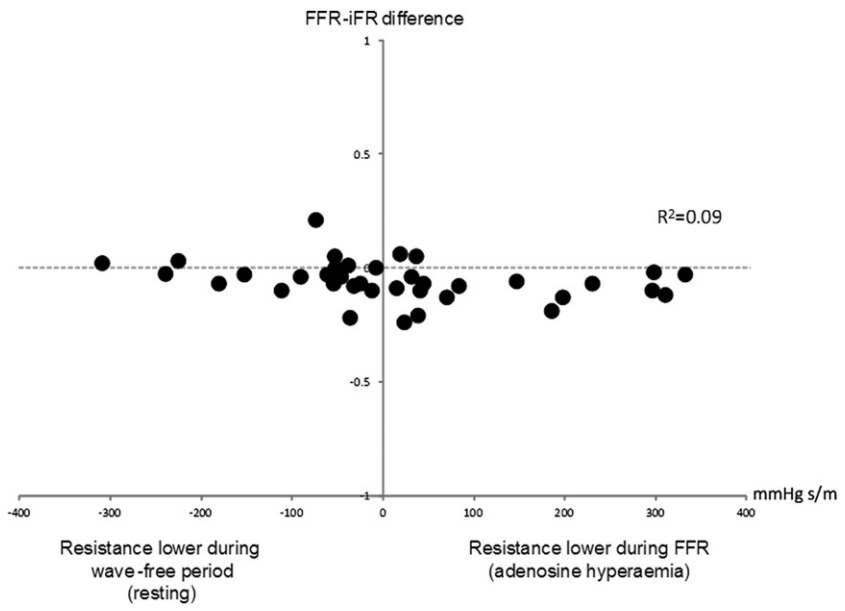

Figure 1 **Difference Between FFR and iFR Compared With the Difference in Resistance During Calculation of Both Indices**

The graphic reveals that resistance is lower in the wave-free period in approximately 50% of cases (left of zero), and lower during adenosine hyperemia in approximately 50% of cases (right of zero). No significant trend is identified to account for the numerical difference between instantaneous wave-free ratio (iFR) and fractional flow reserve (FFR).

As an overall comment, our aim was not to propose a pressure-derived index superior to FFR in the detection of ischemia-generating stenoses, something that was already achieved by diastolic FFR (6), but to tackle the problems that impede adoption of pressure-derived physiology, in particular adenosine administration, recently acknowledged by Pijls et al. (7) as the last remaining barrier for routine use of FFR.

We are impressed by the study alluded to by Dr. Pijls and colleagues, performed in such a large number of patients; again, we are thankful for the interest shown by the correspondents in testing our observations thoroughly. However, we cannot comment on its results before seeing a peer-reviewed full publication reporting in detail the methodology and algorithms used to measure iFR, which, we believe, could be at variance with the methodology applied in our paper, thus explaining the different results of the correlation.

Finally, we agree with the correspondents that further validation of iFR is required before it can be recommended as an additional tool in the clinical domain. To facilitate the achievement of this, we wonder if the investigators would consider allowing the digital data of the recently terminated FAME 2 trial to be analyzed, using the validated iFR algorithm, by a mutually agreed, distinguished neutral party? An understanding of iFR in such a cohort would be invaluable in progressing toward our shared aim of increasing the adoption of physiologically guided revascularization.

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